PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :
A61K 45/06, 31/00, 33/06
A61K 37/02 // A01N 1/02

A1

(11) International Publication Number: WO 86/ 00812

(43) International Publication Date: 13 February 1986 (13.02.86)

(21) International Application Number: PCT/SE85/00296

(22) International Filing Date: 30 July 1985 (30.07.85)

(31) Priority Application Number: 8403912-2

(32) Priority Date: 30 July 1984 (30.07.84)

(33) Priority Country: SE

(71) Applicant *(for all designated States except US)*: PHARMACIA AB [SE/SE]; Rapsgatan 7, S-754 50 Uppsala (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : ARFORS, Karl-Erik [SE/SE]; Skogsmyrsvägen 5, S-752 45 Uppsala (SE). GERDIN, Bengt [SE/SE]; Björkhagsvägen 27 B, S-752 46 Uppsala (SE).

(74) Agent: FOGELBERG, Lennart; Stenhagen Patentbyrå AB, Karlavägen 18, S-114 31 Stockholm (SE).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.

Published
With international search report.

(54) Title: A DRUG KIT OR DRUG COMPOSITION FOR USE IN PREVENTING AND TREATING ISCHAEMIC CELL DAMAGE AND PREPARATION THEREOF

(57) Abstract

A drug kit or drug composition for use in preventing and treating ischaemic cell damage comprises: a) at least one plasma volume expander; b) at least one low molecular, physiologically acceptable hydroxyl radical scavenger; c) at least one physiologically acceptable and water-soluble magnesium salt; and d) at least one organic compound active as a calcium blocking agent dissolved in a carrier, either *per se* or in one or several combinations.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GA**	Gabon	**MR**	Mauritania
AU	Australia	**GB**	United Kingdom	**MW**	Malawi
BB	Barbados	**HU**	Hungary	**NL**	Netherlands
BE	Belgium	**IT**	Italy	**NO**	Norway
BG	Bulgaria	**JP**	Japan	**RO**	Romania
BR	Brazil	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SN**	Senegal
CH	Switzerland	**LI**	Liechtenstein	**SU**	Soviet Union
CM	Cameroon	**LK**	Sri Lanka	**TD**	Chad
DE	Germany, Federal Republic of	**LU**	Luxembourg	**TG**	Togo
DK	Denmark	**MC**	Monaco	**US**	United States of America
FI	Finland	**MG**	Madagascar		
FR	France	**ML**	Mali		

A drug kit or drug composition for use in preventing and treating ischaemic cell damage and preparation thereof.

The present invention relates to a drug kit or drug composition for use in preventing and treating ischaemic cell damage.

When circulation of the blood collapses and ischaemia occurs in peripheral body organs, particularly in the brain, a large number of pathophysiological changes take place. In present clinical practice it is only possible to treat measurable pathophysiological changes, for example changes in blood volume, impaired cardiac function, central acidosis, etc. In such cases each change has been treated individually and it can be said generally that present day therapy for the resuscitation of an organ is mainly directed towards re-establishing blood circulation.

The present invention is based on the concept that incurable tissue damage can be caused as a result of unfavourable conditions created when re-establishing the blood circulation to a body organ.

According to one aspect of this concept the transportation of calcium into and out of a cell is of great significance. The transportation of calcium into and out of a cell normally takes place while maintaining externally of the cell a calcium concentration which is 1000 times greater than the calcium concentration inside the cell. When a deficiency in energy occurs as a result of ischaemia, the calcium gradient cannot be maintained, and calcium will consequently leak into the cell. Calcium is taken up in the cell by the mitochondria, resulting in serious disturbances in energy production. When blood again starts to flow, calcium will enter the cell in still greater quantities, while transportation of calcium from the cell is impaired due to the fact that the build-up of energy in the cell is inhibited by the high calcium content thereof. This greatly increases the load on the mitochondria, which can lead to incurable cell damage and cell death.

According to another aspect of the concept there occurs during the ischaemic period a gathering of degradation products, such as hypoxanthine, which when oxygen is supplied in connection with the re-establishment of circulation are converted by certain enzymes, such as xanthine oxidase, in processes which produce free hydroxyl radicals as a secondary product, possibly via O_2-radicals. Those enzyme systems which protect the tissue from the hydroxyl radicals are not able herewith to deal with the radicals at the rate in which they are formed, which can lead to damage of blood vessels for example.

On the basis of these concepts concerning incurable tissue damage, there is now provided a drug kit or drug composition which provides a better result and enables persons who are subjected to the risk of ischaemic cell damage to be treated in a simplified manner.

The drug kit or drug composition according to the invention is characterized in that it comprises

a) at least one plasma volume expander;
b) at least one low molecular, physiologically acceptable hydroxyl radical scavenger;
c) at least one physiologically acceptable and water soluble magnesium salt; and
d) at least one calcium blocking organic compound

dissolved in a carrier, either per se or in one or more combinations.

The invention is described hereinafter with reference to a drug kit intended for single-unit administration, although the invention also relates to different stock solutions which might come into question.

The plasma volume expander used may be a physiologically acceptable high molecular substance known per se in the expansion of blood plasma volume. These substances have an average molecular weight $\bar{M}_w$ (weight average value) which is higher than 10,000 Daltons, e.g. higher than 15,000 and preferably higher than 30,000 and lower than 400,000 and preferably

lower than 300,000 Daltons. It is well known in the art that the average molecular weight $\bar{M}_w$ chosen depends on the high molecular substance used. Examples of such plasma expanders are plasma-albumin and substances based on dextran, starch derivatives or gelatine derivatives. The dextran products normally have an average molecular weight $\bar{M}_w$ within the range of 30,000 to 80,000 Daltons. Examples of starch derivatives for this purpose include hydroxyethyl starch having an average molecular weight $\bar{M}_w$ within the range of 40,000 - 400,000 Daltons, e.g. in the order of 200,000 Daltons. A number of different gelatine derivatives of varying average molecular weights $\bar{M}_w$ are also used for this purpose. (A review of some plasma volume expanders is found, for example, in the book "Blood Replacement" by U.F. Gruber, Springer Verlag, Berlin-Heidelberg-New York 1969). Of these plasma volume expanders, those based on dextran are primarily preferred.

The concentration of plasma volume expander in the solution in which it is present is chosen so that subsequent to being optionally mixed with one or more solutions incorporated in the kit, the solution injected into the patient will have a plasma-volume-expander concentration which is normal in the use of the substance in question. The plasma volume expander solution of the invention usually has a concentration of 1-15 g/100 ml, such as 2-12 g/100 ml, for example 3-10 g/100 ml.

A common requirement of the hydroxyl radical scavengers which can be used in accordance with the invention is that they are physiologically acceptable and have a molecular weight beneath 10,000 Daltons, preferably beneath 1,000 Daltons. Hydroxyl radical scavengers which have a molecular weight above 10,000 Daltons as a rule have a poor effect. A suitable hydroxyl radical scavenger is soluble in water at physiological pH and ion strengths. It normally includes a functional structure selected from aromatic or aliphatic thiol (-SH), alcoholic and phenolic hydroxyl (-OH) and nitrogen-containing structures, such as primary amine ($-NH_2$) secondary amine (-NH-) and imine (=NH). The hydroxyl radical scavenger

is advantageously selected from the group comprising physiologically acceptable sugar alcohols, monosaccharides, oligosaccharides, amino acids which contain mercapto groups, and methionine and histidine. Among the group of sugar alcohols, mannitol is the primary choice, because it is able to function simultaneously as a diuretic and an anti-oedema agent. Other sugar alcohols of interest in this context are sorbitol and xylitol. Examples of physiologically acceptable monosaccharides are glucose and fructose, and of oligosaccharides malto-oligosaccharides and isomalto-oligosaccharides (which can be obtained by means of partial hydrolysis of starch and dextran respectively), e.g. maltose. Cysteine is an example of amino acids which contain mercapto groups.

The hydroxyl scavenger used is preferably a combination of at least one sugar alcohol and at least one amino acid according to the above, particularly a combination of mannitol and L-methionine, or of mannitol, L-methionine and histidine.

The concentration of hydroxyl radical scavenger is determined by the specific substance in question and by the amount it is desired to administer. It is always so high as to enable a therapeutically active quantity to be administered when the kit is used. The drug kit or drug composition according to the invention may thus contain from 1 g up to 150 g hydroxyl radical scavenger. The range of 1-10 g is particularly applicable in the case of methionine and histidine and a range of 5-150 g in the case of sugar alcohols, calculated per occasion of treatment.

Magnesium salt present in the composition comprises one or more salts from the group water-soluble, pharmaceutically acceptable magnesium salts. Examples of magnesium salts which are thus comtemplated are magnesium sulphate and magnesium chloride. Magnesium chloride is particularly preferred. Water-soluble magnesium salts are present in the composition according to the invention in quantities corresponding to 5-100 mmol Mg^{2+}, calculted per occasion of treatment.

The organic compounds acting as calcium blockers are normally of low molecular weight, with a molecular weight beneath — 2000 Daltons. They are defined by their ability to prevent the migration of calcium ions into cells. Cf. "Calcium Blockers" (edited by Flaim, S.F. et al; Urban-and Scharzenberg. Baltimore-Munich, 1983). The compounds in question may be of highly different structure, niphedipine, nimodipine, verapamil, diltiazem, lidoflazine, flunarazine and analogous compounds can be mentioned by way of example. The calcium blockers used in accordance with the invention may be soluble in water and/or in fat. Verapamil(5-[(3,4-dimethoxyphenylethyl) methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile) is an example of a water-soluble calcium blocker, while an example of a fat-soluble calcium blocker is lidoflazine(4-[4,4-bis(4-fluorophenyl)butyl]-N-(2,6-dimethylphenyl)-1-piperazine acetamide). When a fat soluble calcium blocker is used in accordance with the invention, it is advantageously included in the kit as a component separate from the plasma volume expander. According to one aspect of the invention, this enables lidoflazine to be administered in a separate injection when using the drug kit. In this variant of the invention, the fat-soluble calcium blocker may be dissolved in, for example,:

I. A mixture of water and ethanol in an amount which is physiologically acceptable for the purpose. When the calcium blocker has the nature of an amine, the mixture can be acidified, to increase solubility. It is essential in this respect that acidification of the mixture is adapted to the pH and buffer capacity of the remaining kit components to be used on the occasion of the treatment. The mixture is advantageously acidified with acetid acid, hydrochloric acid, or some other physiologically acceptable acid. The mixture may also contain glycerol.

II. Physiologically acceptable fat emulsions used for parenteral nutrition (a number of such emulsions are described, inter alia, in patent literature; cf. for example the U.S.

Patent Specification No. 4,168,308).

A usable product in this connection is retailed under the name Intralipid® by Apoteksvarucentralen Vitrum AB, Stockholm, Sweden. This product contains fractionated soya oil in an amount of 100 or 200 mg/ml, fractionated egg-phospholipides (as stabilizer) in an amount of 12 mg/ml, and glycerol in an amount of 25 mg/ml, with the remainder sterile water.

III. Physiologically acceptable emulsions of fluorinated hydrocarbons, which are administered parenterally due to their ability to dissolve and transport oxygen gas.

The amount of calcium blocker included in the kit varies from substance to substance. Calculated per occasion of treatment it is normally included in amounts of from 1 to 300 mg; a particular value for lidoflazine is from 10 to 200 mg.

The carrier or vehicle in which the active kit components can be dissolved is physiologically acceptable and contains water. It may optionally be buffered with a physiologically acceptable buffer substance to a pH-value and an ion strength such that the total effect of that intended to be administered is physiologically acceptable. This means that in the selection of a suitable buffer system, attention is paid to all components included in the kit or the composition according to the invention. Examples of buffer systems include trometamol buffers, carbonate buffers, phosphate buffers, histidine buffers, acetate buffers and combinations thereof. According to the invention a buffer system may be included as a solution separate from the solution containing the plasma volume expander, hydroxyl radical scavenger, magnesium salt. A separate buffer system shall be used when acidose is present. It shall be capable of restoring the blood of the patient in question to a pH-value of from 7.0 to 8.0, preferably the physiological pH-value 7.4. The buffer capacity lies in the region of 25-300 mmol, preferably 50-200 mmol. In practice this means that a separate buffer system shall have a pH-value

in the range of 7.0 - 10.0, preferably 7.4 - 9.2.

The drug kit or composition according to the invention preferably also includes a diuretic agent, particularly an osmotic diuretic agent, and/or an anti-oedema substance. Since in addition to being an hydroxyl radical scavenger, mannitol is also able to fulfil the function of both a diuretic and an anti-oedema substance, mannitol is a preferred substance in the present context. Sorbitol or glycerol can be used as a diuretic agent, either instead of or together with mannitol. The quantities in which a diuretic agent and anti-oedema substance is used is dependent on the substance utilized, and may thus vary within wide limits. In the case of an osmotic diuretic agent, the quantities used may lie within the range 5-150 g, otherwise 0.1-200 mg. In the case of the anti-oedema substance a corresponding range may be 5-150 g.

It may also be of advantage to incorporate in the kit or the composition according to the invention an xanthine oxidase inhibitor, such as allopurinol for example, (50 mg - 5 g, depending on which is chosen), and/or a superoxide radical scavenger, such as superoxide dismutase for example, and/or an hydrogen peroxide inactivator, such as catalase for example, and/or a substance which binds iron in a solid complex, such as desferrioxamine or diethylenetriamine-pentaacetic acid or ethylenediamine-di(o-hydroxyphenylacetic acid), or a phytic acid derivative.

The quantities quoted above in respect of the diuretic agent, anti-oedema substance and xanthine-oxidase inhibitor apply to each occasion of treatment.

The active components included in the drug kit or drug composition are present in the form of a single solution or a plurality of solutions. Precisely how they are combined is determined, inter alia, on the grounds of solubility and stability, even though for practical reasons the aim is to place

them in a common solution. For example, in accordance with one advantageous variant, the plasma volume expander, hydroxyl radical scavenger, magnesium salt and calcium blocker are selected so as to be compatible with one another in solubilized form and with the desired pH-value of the solution to be administered. Similar considerations are applicable to remaining active components such as the anti-oedema substance, diuretic agent, xanthine-oxidase inhibitor, superoxide radical scavenger, hydrogen peroxide inactivator and iron-binding substance.

On the basis of those studies carried out hitherto, the embodiment most preferred has a solution (A) which contains plasma volume expander, hydroxyl radical scavenger and magnesium salt; a solution (B) which contains a buffer system and a solution or dispersion (C) which contains a fat-soluble calcium blocker. In this embodiment, the remaining active components are placed in one of the solutions A, B or C. For example, if allopurinol is chosen as the xanthine-oxidase inhibitor, it can be added to the buffer solution B for reasons of solubility. If the kit does not include such a solution, it may be necessary to choose another xanthine-oxidase inhibitor.

The various solutions included in a drug kit according to the invention (and in certain cases the dispersion of organic calcium blocker) may have the form of sterile storage solutions from which a suitable quantity of the separate solutions or dispersion is taken on each treatment occasion; preferably, however, the kit is made up with dosages suited to the purpose, each dosage containing therapeutically active quantities of the substances in question. In this latter case a solution (A) according to the aforegoing can be packed into units of 100-1000 ml, normally 500 ml, a solution (B) packed in units of 10-100 ml, preferably 25-100 ml, and a solution or dispersion (C) packed in units of 5-50 ml, preferably 10-30 ml. The units can be poured into plastic sachets, glass or plastic bottles, ampoules, syringes etc.. The exact choice varies from case to case, and is determined, inter alia, by practical considerations. It can be mentioned by way of example that the solution C is advantageously placed in an ampoule or disposable

syringe.

The concentration in which the active components are present are selected so as to maintain the mutual proportions between the aforementioned quantities. In the aforesaid preferred embodiments, the concentration of hydroxyl radical scavenger and magnesium salt corresponds to the aforementioned quantities per 500 ml of solution. The same applies to the calcium blocker, when it is incorporated in the same solution as these two substances. When it is present in a separate solution (C), the calcium blocker concentration may be from 10 to 100 times greater than in the previous case, due among other things to the solubility conditions.

When calculated on the basis of a patient weighing 70 kg, the kit components are normally administered to the patient in a total solution volume of 500-600 ml.

When using a drug kit according to the invention in which the calcium blocker is included as a separate unit (C), this unit is the first to be injected into the patient. It is desirable that this injection can be given relatively quickly. In those cases where metabolic acidose prevails, as with a cardiac arrest for example, solution (B) is used to correct the pH of the patient. The solution (B) may be mixed with the solution (A) immediately or shortly before being used. The mixture, or the solutions (A) and (B) each per se, is or are then administered to the patient as soon as possible after having injected the patient with (C). In the absence of metabolic acidose, only solution (A) is administered.

When using a drug composition according to the invention in which a plasma volume expander, an hydroxyl radical scavenger, magnesium salt and a calcium blocker are present in a common solution separate from a buffer solution (B), this common solution is injected into the patient separately or in mixture with (B). The solution (B) is only used in the case of metabolic acidose.

The drug kit according to the invention is intended for use primarily in acute resuscitation, such as in the event of a cardiac arrest or in other situations in which blood circulation collapses and the brain is subjected to ischaemia. The drug kit can also be used in various kinds of trauma in the central nervous system, cerebral haemmorrhage, apoplectic strokes, subarachnoidal bleeding, or in the case of intracranial vessel surgery, where blood vessels must be temporarily closed. The drug kit can also be used with ischaemic conditions in other body organs, such as the heart, kidneys, intestines and skeleton muscle, in conjunction with shock, trauma, embolies and heart attacks, and also in surgical operations, such as heart surgery, vessel reconstruction and organ transplantation.

The drug kit can also be used as a perfusion solution and preserving solution for body organs in, for example, cardioplegy or organ transplantation.

The invention also relates to a process for the preparation of a drug kit or drug composition which process is characterized by the features set forth in claim 11.

The invention also relates to a method of treating the aforesaid conditions. In such a treatment the components of the kit are administered in any of the ways described above.

The invention will now be described with reference to a number of working examples.

EXAMPLE 1

Preparation of a drug kit

Solution A

15 g dextran having an average molecular weight ($\bar{M}_w$) of about 60 000, 4.0 g $MgCl_2$ (anhydrous), 25 g mannitol, 5 g L-methionine, and 5 g L-histidine were dissolved in 500 ml distilled water. The resultant solution was sterilized by sterile filtration and poured into a 500 ml sterile plastics bag, which was then sealed under aseptic conditions.

Solution B

There were used for this solution 50 ml of a conventional commercial buffer solution having a pH of 9.2 and containing 20 g trometamol with a buffer capacity of 150 mmol (Addex® THAM form Pharmacia Infusion AB, Uppsala, Sweden).

Solution C

80 mg lidoflazine were dissolved in 1.0 g ethanol (99.5%), 0.1 g concentrated acetic acid and 1.5 g glycerol, and was diluted up to 10 ml with distilled water. The solution was sterilized by sterile filtration and poured into a 10 ml ampoule under aseptic conditions.

The solutions A, B and C were then packed in a box, as a unit.

EXAMPLE 2

Pharmacological tests

The tests were carried out with a rat model, which gives an incomplete cerebral ischaemia with a cortical flow < 5% of the normal flow, and a flow in the brain stem which is about 30% of the normal flow. This is effected by squeezing the two carotid arteries while simultaneously lowering the blood pressure to 50 mm Hg, by bleeding. The method has been described by Nordström C.H. and Siesjö B.K., Stroke 9, 327-335 (1978).

Wistar-rats weighing 300-400 g and fasted overnight were used in the tests. The rats were anaesthetized with 4% Fluothane® (ICI-Pharma AB, Gothenburg, Sweden), 30% O_2/70% N_2O, intubated and connected to a respirator. The vena jugularis externa was uncovered. Celocurine (5 mg/kg) was injected and a catheter was placed in vena cava superior. Catheters were also placed in the tail artery and in a tail vein for measuring blood pressure and infusion, respectively. EEG-electrodes were applied and finally 5 ml 0.9% NaCl were administered intraperitoneally and 100 IU heparin intravenously. The supply of Fluothane® was cut-off, whereafter blood gases, pH and the

sugar content of the blood were measured for a period of at least 30 minutes. It was endeavoured to obtain a pH in the region of 7.35 - 7.40, pCO_2 of 4.67 - 5.50 kPa, and pO_2 of 11.0 - 18.0 kPa, and a bloodsugar content in the region 3.0 - 8.0 mmol/l. If these criteria were not attained, the animal was excluded.

The following procedure was undertaken in order to create ischaemia:

A solution of trimethaphan-D-camphorsulphonate in sterile water (15 mg/ml, Arfonad ®, from Hoffmann-La Roche & Co AG, Basle, Switzerland) was administered intravenously, until the average blood pressure was 80 mm Hg, whereafter the two carotid arteries of respective animals were shut-off and blood was drained from the animals through respective catheters in vena cava superior until an average blood pressure of 50 mm Hg was reached.

The EEG was recorded continuously during this time period, and the ischaemic period was taken to commence when an isoelectric EEG was obtained. Subsequent to an ischaemic period of 10 mins, the infusion of lidoflazine in the treatment group was commenced. Of a total dosage of 1.0 mg in one ml of a physiological sodium chloride solution, half was administered during the ischaemia and the remainder after 5 minutes recirculation. A corresponding volume of physiological sodium chloride solution was administered to a control group. Infusion of an aqueous solution containing 3.5% albumin, 10% mannitol, 2% L-methionine, 92.2 mM magnesium chloride and 0.5 M Tris (percentages given in w/v), was commenced during the last two minutes of the ischaemic period and was continued for two minutes during the recirculation phase. A total of 2 ml were injected. The blood pressure was monitored during the infusion period and adjusted when necessary, by bleeding the animal or infusing blood thereinto. The rats were left in the respirator until they began to waken, whereupon they were ventilated for two minutes with 100% oxygen gas and the respirator then disconnected. Tracheal tubes and oxygen masks were left in position until

stable breathing was observed.

Of 10 test animals in each group, the mortality of the control group was 60%. The corresponding figure in the group treated with a drug kit according to the invention was 20%. No significant differences were observed with regard to average arterial blood pressure, blood gas or blood sugar. With regard to the pH of the blood, it was observed that the blood-pH of the animals in the group treated with a drug kit according to the invention fell after the ischaemic period to a lesser extent than that of the animals in the control group, this being attributed to the buffer capacity of the drug kit according to the invention.

C L A I M S

1. A drug kit or drug composition for use in preventing and treating ischaemic cell damage, characterized in that it contains:

   a) at least one plasma volume expander;
   b) at least one low molecular, physiologically acceptable hydroxyl radical scavenger;
   c) at least one physiologically acceptable and water-soluble magnesium salt; and
   d) at least one organic compound active as a calcium blocking agent

dissolved in a carrier, either per se or in one or several combinations.

2. A drug kit or composition according to Claim 1, characterized in that the plasma volume expander is plasma-albumin or is based on dextran, a starch derivative or gelatin derivative.

3. A drug kit or composition according to Claim 1 or Claim 2, characterized in that the hydroxyl radical scavenger comprises one or more substances from the group physiologically acceptable sugar alcohols, monosaccharides, oligosaccharides, amino acids which contain mercapto groups, methionine and histidine.

4. A drug kit or composition according to any one of Claims 1-3, characterized in that the magnesium salt is magnesium sulphate or magnesium chloride.

5. A drug kit or composition according to any one of Claims 1-4, characterized in that the calcium blocker is lidoflazine.

6. A drug kit or composition according to any one of Claims 1-5, characterized in that it also includes a diuretic agent and/or anti-oedema substance.

7. A drug kit or composition according to Claim 6, characterized in that the diuretic agent is mannitol and/or sorbitol.

8. A drug kit or composition according to Claim 6, characterized in that the anti-oedema substance is mannitol.

9. A drug kit or composition according to any one of Claims 1-8, characterized in that it also includes an xanthine oxidase inhibitor and/or a superoxide radical scavenger and/or a hydrogen peroxide inactivator and/or an iron-binding substance.

10. A drug kit or composition according to any one of Claims 1-9, characterized in that it also includes a physiologically acceptable buffer system.

11. Process for the preparation of a drug kit or drug composition for use in preventing and treating ischaemic cell damage, characterized by dissolving

a) at least one plasma volume expander;
b) at least one low molecular, physiologically acceptable hydroxal radical scavenger;
c) at least one physiologically acceptable and water-soluble magnesium salt; and
d) at least one organic compound active as a calcium blocking agent

in a carrier, either per se or in one or several combinations.

INTERNATIONAL SEARCH REPORT

PCT/SE85/00296

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

A 61 K 45/06, 31/00, 33/06, 37/02 // A 01 N 1/02

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC 2,3,4	A 61 K 31/00, /495, /715, 33/06, /14, 37/02, 45/06; A 01 N 1/02
IPC 1	A 61 K 27/10 .../...

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
Y,X	CH, A5, 624 579 (BEHRINGWERKE AG) 14 August 1981, see especially the examples & NL, 7607737 FR, 2317943 DE, 2532183 BE, 844286 LU, 75393 US, 4061537 GB, 1556199 JP, 52028485 SE, 7608183	1-11
Y,X	EP, A1, 0 012 272 (DR FRANZ KÖHLER CHEMIE KG) 25 June 1980, see inter alia the claims and page 2, lines 25-28 & AT, 503 CH, 639270	1-11
Y,X	EP, A1, 0 054 635 (DR FRANZ KÖHLER CHEMIE KG) 30 June 1982, see inter alia	1-11

.../...

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1985-10-07	1985 -10- 11
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Martin Hjälmdahl Martin Hjälmdahl

L.E

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II Fields searched (cont).

US Cl 424:154, 180, 250

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	the claims and page 7, line 14-page 8, line 9 & US, 4415556 CA, 1170994 AT, 11736	
Y,X	EP, A1, 0 085 033 (PHARMACIA AKTIEBOLAG) 3 August 1983, see especially page 3, lines 1-5, 23-29, and page 4, lines 13-23 & WO, 83/02391 SE, 8200252 AU, 11058/83 EP, 0098853	1-11
A,Y	US, A, 4 407 801 (SCIENCE UNION ET CIE) 4 October 1983, see especially column 2, lines 38-40 & BE, 890568 GR, 2084019 FR, 2490963 LU, 83654 DE, 3139005 AU, 75744/81 CA, 1169775 CH, 650675	1-11
P	WO, A, 84/03623 (H BLOCH) 27 September 1984, see especially claims 9-11 and page 7, the second paragraph.	1-11
Y,X	E Schröder et al, "Pharmazeutische Chemie", published 1982, by Georg Thieme Verlag (Stuttgart), see pages 660-661	1-11
Y,X	Federation Proceedings, Vol. 40, No 14, issued December 1981 (Washington) S F Flaim & R Zelis "Clinical use of calcium entry blockers", see pages 2877-2881, especially page 2877 (abstract) and page 2880, the second column ("Lidoflazine")	1-11
Y,X	Chemical Abstracts, Vol 92 (1980), abstract No 15670s, Surg. Forum 1979, 30, 435-7 (Eng.)	1-11